REMARKS/ARGUMENTS

Claims 1 and 15 have been amended to recite that the probes are immobilized to at least one support as described at p. 13, lines 16 and 17, and p. 14, lines 5-13. These claims have also been amended to specify that the probes span the reference sequence or estimated target sequence as described at e.g., p. 6, lines 5-10. Applicants respond to the Examiner's comments using the paragraph numbering of the office action.

3. Claim 15 has been amended to replace "the" with --a--.

5. The claims have been amended to recite that the probes are immobilized.

6. Claims 1-3 and 5-15 stand rejected as allegedly anticipated by Drmanac. Applicants respectively traverse, particularly, insofar as the rejection might be applied to the amended claims. Drmanac does not disclose immobilized probes in his proposed methods nor the iterative use of arrays of probes respectively spanning a reference sequence to estimate a target sequence. Regarding the Examiner's other comments, it is noted that much of the Drmanac reference is directed to de novo sequencing as distinct from detecting a mutations in an otherwise known sequence. The Examiner's citations to the Drmanac patent do not distinguish between these distinct embodiments. For example, the Examiner relies on col. 4, lines 66-67 for designing an array of probes based on a reference sequence. However, this section of the patent is describing a "universal" set of probes (col. 4, lines 57). Even though some such sets do not contain every probe they are "still sufficient for reading every bp in any sequence with at least one probe" (sentence bridging cols. 4-5). A universal array that can read every base in any sequence is the antithesis of an array designed based on a particular sequence (i.e., a reference sequence or an estimate of a target sequence, as claimed). For at least these reasons, the Examiner has not established anticipation of pending claims.

Regarding claim 2, the Examiner points to col. 13, lines 5-17 as disclosing repeating steps (e)-(h) until the estimated sequence is constant. However, the section of the patent cited by the Examiner is referring to de novo sequencing using a universal array (see col. 12, lines 60). Thus, the cited disclosure does not occur in the context of the claimed methods in which an array is designed based on a reference sequence or an estimate of a target sequence.

Regarding claim 3, the Examiner appears to regard an allelic variation as being the same as a species variation. This is not the case. An allelic variation is a variation between individuals of the same species, whereas a species variation is a variation between species.

Regarding claims 5-6, a single base mutation in a target sequence does not necessarily mean the target sequence shows 80-95% identify with a reference sequence. This could be the case only if the target sequence was no more than 20 bases long. In fact, the target sequence referred to at col. 3, line 3 is 1000 bp and no specific length is mentioned in Example 8. Moreover, the discussion at col. 3, line 3 occurs in the context of de novo sequencing by hybridization using universal arrays. The discussion at Example 8 occurs in the context of a conventional detection of mutations using probes. Although the Example refers to performing "4 cycles," the cycles are performed simply to allow multiple hybridizations to the same sample. There is no suggestion of designing a new set of probes based on an estimated sequence derived from a previous hybridization.

Regarding claim 7, the cited section of the Drmanac patent, Example 16 refers to de novo sequencing by hybridization. This example contains no mention of designing oligonucleotides to be complementary to a reference sequence, as claimed. Rather, the oligonucleotides appear to be part of a universal set of the type described in Example 1.

7-8. Claim 4 stands rejected as allegedly obvious over Drmanac in view of Dietrich. Dietrich is cited as teaching that comparison of human and primate target sequences is useful for study of HIV genotherapeutics. This rejection is respectfully traversed. Claim 4 is distinguished over the combination of references for the same reasons as it is distinguished over Drmanac alone. In addition, it is respectfully submitted that the asserted motivation of a benefit

of comparing human and primate target sequences would not have led one to modify the teaching of Drmanac to analyze a primate sequence based on a human reference sequence (or vice versa). To "establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the *specific* combination that was made by the applicant." *In re Dance,* 160 F.3d 1339, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis supplied). Here, the alleged benefit of comparing human and primate sequences would arise regardless of how the sequences are determined, and provides no indication as to how the sequences should be determined. Thus, one reading Dietrich wanting to sequence additional primate or human sequences would not have been provided any reason to depart from the many conventional methods of determining sequences including dideoxy sequencing and Maxam Gilbert sequencing. As the Federal Circuit has cautioned, a "person of ordinary skill is the art is...*presumed to be one who thinks along the lines of conventional wisdom in the art...*," *Standard Oil Co. v American Cyanamid Co.*, 774 F.2d 448 (Fed. Cir. 1985), at p. 454 (emphasis added).

9. Claim 15 stands rejected as allegedly obvious over Skiena in view of Drmanac. Skiena is cited as disclosing a method of analyzing a target nucleic acid comprising designing an array of probes complementary to an estimated sequence of a target sequence. The Examiner acknowledges Skiena is silent regarding the content of the target sequence being sequenced. Drmanac is cited as teaching sequencing of variants of known target sequences. The Examiner takes the view that it would have been obvious to apply the sequencing of Skiena to a sequence variant based on Drmanac's alleged teaching regarding the importance of diagnosing and identifying sequence-specific diseases and traits. This rejection is respectfully traversed.

Skiena discusses a method of sequencing by hybridization that is intended to be general to any type of target sequence. Initially, the target sequence is hybridized to a universal sequencing array containing all probes of a given length (col. 6, lines 41-42). Subsets of positively and negatively hybridizing probes are then determined (col. 6, lines 45-48). A second array is then designed based on combinations of probes from the positively hybridizing subset

(col. 6, lines 49-61). The hybridization is then repeated and subsets of positively and negatively hybridizing probes again determined (col. 6, line 61 to col. 7, line 5). The process is repeated until the cumulative hybridization data reveals the identity of the target sequence (col. 7, lines 9-15).

Claim 15 specifies a step of designing an array based on a target nucleic acid having a sequence, which is a variant of a reference sequence. Skiena's method starts with a universal sequence array containing all probes of a given length and is intended to analyze a target without any prior knowledge of its identity. As discussed at greater length in the appeal brief, there was no motivation to alter Skiena's approach, in favor of designing an array to comprise a set of probes having complementarity to the known reference sequence. To do so would forfeit the utility of Skiena's own method for an analyzing any kind of target sequence. Moreover, the remaining steps in Skiena method which are intended for analyzing a target sequence without any prior knowledge as to its identity would seem unnecessarily complex for the simpler task of analyzing a variant of a known sequence.

The Examiner alleges that motivation is found in Drmanac's discussion regarding detecting variants. However, to "establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the *specific* combination that was made by the applicant." *In re Dance,* 160 F.3d 1339, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis supplied). Motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood,* 28 USPQ2d 1300, 1302 (BPAI 1993). Insofar as Drmanac mentions detecting variations of a reference sequence, he is referring to a task for which many standard methods s including use of allele-specific probes, allele-specific primers, a single-base extension reaction, dideoxy sequencing, conformational testing, and so forth. This motivation provides no reason that the skilled artisan would depart from any of the standard methods in favor of that discussed by Skiena. The Skiena method would probably have appeared to be unnecessarily complicated both theoretically and practically for performing a simple task for which many routine methods of analysis were available. Accordingly, it is submitted that the

asserted motivation would not have impelled the artisan to combine the teaching of Drmanac with Skiena.

Additional distinctions over Skiena explained in the appeal brief and the last response have not been addressed, and are reiterated here. Skiena's does not discloses a step of estimating the sequence of a target nucleic acid. The Examiner takes the view that such is disclosed by step (d) of claim 1. However, step (d) does not recite "estimating" a sequence. Indeed the word "estimating" is not found in the entire Skiena patent. Rather claim 1(c) of Skiena requires identifying a set of hybridizing oligonucleotides, and step (d) recites selecting a second set of oligonucleotides based on the hybridization of the first set. Neither step (c) or (d) refers in any way to the reconstruction of an estimated sequence from the set of positively hybridizing oligonucleotides. To say that a set of positively hybridizing oligonucleotides itself constitutes a sequence without any attempt being made to orient the oligonucleotides with respect to each other would be akin to saying that a restriction mapping of a target reveals its sequence. Such would be abhorrent to usage in the art whereby a restriction map or set of hybridizing oligonucleotides may be regarded as being a fingerprint but is not a sequence.

Skiena also does not disclose reestimating the sequence of a target nucleic acid. The Examiner refers particularly to claim 2 of Skiena for such disclosure. However, the claim refers to "determining" the sequence of a target not reestimating it. In Skiena's initial iterations of his method, he does not disclose estimating a target sequence but rather identifies a subset of hybridizing probes. In the final step of Skiena's method he does not estimate a target sequence, but rather determines the sequence uniquely. In Skiena's view at least, the determined sequence is correct and not an estimated, much less a reestimated sequence (col. 7, lines 12-15).

The Examiner's position may in part be based on the view that simply determining a set of hybridizing oligonucleotides itself constitutes "estimating the sequence of a target," under a broad interpretation of the claims which the Examiner feels entitled to make during prosecution. In response, applicant submits that the Examiner is not merely interpreting the claims broadly, but effectively reading out explicitly recited claim steps. The present claims recite separate steps of "determining the relative hybridization of the probes to the target nucleic acid," and

"estimating the sequence of the target nucleic acid from the relative hybridization of the probes." Thus, to view "determining the relative hybridization of probes" as being equivalent to estimating a sequence effectively reads out the step of "estimating the sequence" from the claim.

In attempting to rebut applicant's position, the previous Examiner stated that Skiena "inherently teaches both steps of hybridization and estimation the sequence of a target nucleic acid (citing to col. 9, lines 33-49 and col. 4, lines 19-21) (final office action at p. 10). However, "[i]nherency ... *may not be established by probabilities or possibilities.*" *Mehl/Biophile v. Milgraum,* 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (emphasis supplied). "The mere fact that a certain thing *may* result from a given set of circumstances *is not sufficient* to establish inherency." *In re Rijckaert*, 28 USPQ2d 1955 (Fed. Cir. 1993) (emphasis supplied). Here, the previous Examiner's proposal of inherent disclosure of estimating a sequence relies on unsupported assumptions. Thus, when Skiena at col. 4, lines 19-21 refers to resolving "ambiguities" the Examiner is apparently supposing that Skiena has compiled a sequence from his hybridizing oligonucleotides, and is referring to ambiguities in that sequence. However, there is no basis for such an assumption, particularly, when in the example discussed at col. 6, lines 40 to col. 7, line 9, Skiena does not compile a sequence from hybridizing oligonucleotides until all of the hybridizations have completed. Instead, Skiena's "ambiguities" probably refer to ambiguities in the hybridization data due to the same oligonucleotide being complementary to multiple segments of a target sequence (see col. 4, lines 19-20). Col. 9, lines 33-49 of Skiena merely summarizes Table 2 and the number of iterations of Skiena's method needed to determine a sequence for various targets. This is every reason to suppose that these iterations refer to the same process exemplified at col. 6, lines 40 to col. 7, line 9. As noted in this process, Skiena does not determine a sequence at any iteration except the last.

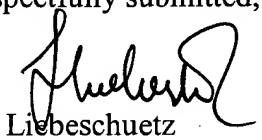
For these reasons, the Examiner has not established under principles of inherency that Skiena necessarily estimates or reestimates a sequence. Insofar as there is doubt, such doubt should inure to the benefit of appellant given that the burden of proof rests with the PTO. Accordingly, applicant maintains that Skiena does not teach "estimating," or "reestimating" a target sequence

Because Skiena does not disclose estimating or reestimating the sequence of a target nucleic acid, it follows that he also does not disclose designing an array of probes based on an estimated or reestimated sequence of a target nucleic acid.

For these reasons, it is respectfully submitted that insufficient motivation has been identified to combine the references, and that the combination of references does not meet all claim limitations.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Joe Liebeschuetz
Reg. No. 37,505

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
Attachments
JOL:sjj

60443283 v1